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In-vitro Characterization of Optimized Multi-Unit Dosage Forms of Theophylline and its Solid State Characterisation

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ABSTRACT: The objective of this study is to compare the drug release profile of an optimized multi-unit dose (MU) tablet consisting of rapid and slow release components, a formulated sustained released tablet and two brands of sustained release tablet formulations in the market with a designed model. The fast release component consisted of conventional granules while the slow release component consisted of wax granules of theophylline. The optimized MU tablets was formed by mixing the conventional and matrix granules in ratio 1:1 and compressed. Parameters evaluated were tablet tensile strength and dissolution studies. The optimized formulation was characterized with Differential Scanning Calorimetry and Fourier-Transform Infrared Spectroscopy. Results showed that the optimized MU tablets gave dissolution profile that was comparable with that of the designed model. The following were the dissolution parameters of the optimized MU formulation: the maximum release (m_∞) = 91%, prompt release dose (m_p) = 24%, time to attain maximum release (t_∞) = 12h and first order release rate constant (k) = 0.20 h^{-1} which is comparable with the release data for the model. The other formulations deviated by giving m_p and t_∞ that were too low compared with those of the model. There were also no drug/excipient interactions. The indication is that the prompt release dose was determined not only by the amount of the rapid release components in the MU dose formulation but also by the amount of sustained release components, attributable to the deformation of granules of rapid components into that of slow release components during tablet formulation.

Keywords: Multiunit dose tablet, theophylline, Differential Scanning Calorimetry (DSC), Fourier-Transform Infrared Spectroscopy (FTIR).

The procedure of delivering a drug is as important as the actual activity of the drug in determining the therapeutic effect. In order to obtain optimum therapeutic effect, the right amount of a drug needs to get to the right place at the right time. Hence, advanced drug delivery formulations have been developed over the past 20 years that do not simply release a drug at a specific rate, but release the drug in a way that the pharmaceutical scientists and engineers have designed (Peppas, *et al.,* 2000). However, since drug delivery can improve safety, efficacy, convenience and patient compliance, improving delivery methods has become a major focus of pharmaceutical companies (Peppas, *et al.,* 2004).

Controlled release in drug delivery can significantly enhance the therapeutic effect of a drug. One of the challenges of pharmaceutical technology is the development of new solid dosage forms for controlled release purposes which will minimize side effects and hence non compliance in the patient (Khan, *et al.,* 2001). Conventional dosage forms produce immediate release of therapeutic active ingredient, which may be considered an initially too high drug release with the attendant risk of side effects. However, the major drawback that may be associated with matrix tablets is a delay in the release of prompt dose to the systemic circulation, hence does not provide the rapid onset of action. These problems can perharps be ameliorated by the design of a multiunit dosage form (Vial–Bernasconi*, et al.,* 1988; Folloniner and Doelker, 1992). A multiunit dosage form (MU) consists of drug particles of different release profiles with respect to onset, rate and maximum release. It is designed in a fashion that a component of the dosage form (i.e tablet or capsule) will give prompt release followed by sustained release. MU provides a prompt dose followed by a constant therapeutic plasma level of the drug, with less frequent administration, thus reducing side effects which will lead to improved patient compliance with medication. This eventally results in a good treatment response. MU are particularly of immense benefit in the management of chronic diseases such as hypertension, asthma, diabetes mellitus and schizophrenia.

Theopylline is a methylxanthine derivative and its chemically name is 1H-Purine-2, 6-dione, 3, 7-dihydro-1, 3-dimethyl-xanthine. The molecular formula of anhydrous theophylline is $C_7H_8N_4O_2$ with a molecular weight of 180.17. It is often indicated in the treatment of asthma (Ukena, *et al.,* 1997). It is rapidly and almost completely absorbed after oral administration in solution or tablet with a bioavailability of 96% (Hendeles, *et al.,* 1977). The biologic half-life of the drug is about 4.5 h and the usual oral dosage regimen is 60 to 200 mg every 3 to 4 h with a maximum dosage of 600 mg/day (Uhumwangho and Okor, 2007). Since asthma is a chronic disease requiring prolonged treatment and

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theophylline having a short half-life, several efforts have been made to develop sustained release dosage forms of the drug. One of such efforts includes the formation of floating lipid pellets of the drug to increase gastric retention and prolong release (Hamdani, *et al.,* 2006).

There are several physical approaches by which drug release from a dosage form can be retarded. One approach which will be considered in the present study is melt granulation, whereby the drug powder is triturated with a melted wax serving as a hydrophobic retard release agent (Uhumwangho and Okor, 2006[a]). The resulting granules consist of the drug particles dispersed in a wax continuous matrix. Hence, the release from such systems usually follows a diffusion controlled mechanism (Uhumwangho and Okor, 2006[a]). Various waxes have been investigated as release retardants including carnauba wax, glyceryl monooleate and its monostearate, beeswax and goat fat (Uhumwangho and Okor, 2006[a]). Of these, carnauba wax was considered most suitable as it produces compressible and free flowing granules (Uhumwangho and Okor, 2006[b]; Uhumwangho et al 2009). It has been used in pharmaceutical industries as tablet coating agent, and more recently as a matrix former in the modification of drug release by melt granulation technique (Uhumwangho and Okor, 2006[a,b,c]). This will therefore be considered for the present study.

Recently, a model of MU of theophylline based on pharmacokinetic parameters of the drug from Official monograph as well as the dosage for a conventional tablet was designed (Uhumwangho and Okor, 2007). In the model, the dosage form had a prompt release dose of 33% in 1h. The remaining 67% in the sustained release component was released slowly at a first order dissolution constant of $0.24h^{-1}$ for the next 12h, hence maximal release (100%) was achieved in 12h. From this study, it was concluded that the MU of ratio (1:1) gave prompt dose (m_p) and maximal release (m_∞) at t_∞ that was comparable with the designed model. Hence, it was considered as the optimized formulation. In this study, the optimized MU (600mg), formulated sustained released and two different market formulations F1 and F2 (each 400mg) will be compared with the designed model.

MATERIALS AND METHODS

Materials: Carnauba wax (Halewood Chemicals Ltd, England) is a fine waxy solid with melting point of $82\text{-}88^0$C, yellowish in colour and was used as the matrix former. Maize starch (Loba Chemie, Bombay, India) was used as binder in the form of mucilage (20% w/v) and as disintegrant in the form of dried powder (5% w/w) in the tablets, while magnesium stearate (Qualikems Fine Chemical Pvt Ltd, India) was used as lubricant at a concentration of 0.5% w/w in the tablet formulations. The test drug was theophylline (Dr Reddy's Laboratories Ltd, India). Two different brands of sustained release formulation of theophylline were purchased from the market. The manufacturing, expiring dates and batch numbers were recorded.

Methods

Melt granulation technique: Carnuaba wax (20 g) was melted in a stainless steel container in a water bath at a temperature higher than its melting point of wax (i.e. 90^0C). A sample of theophylline powder (100 g) was added to the melted wax and thoroughly mixed with a glass rod. It was then allowed to cool to room temperature (35 ± 2^0C).The mass was pressed through a sieve of mesh 10 (aperture size; 710 μm) to produce matrix granules that will not disintegrate in aqueous fluid to their primary (powder) particles.

*Wet granulation technique***:** A sample of theophylline powder (100 g) was wet-massed with starch mucilage (20% w/v). The content of starch binder in the resulting granules was 16.7% w/w. The wet mass was pressed through a sieve of aperture size 1.7 mm, spread thinly on trays and then dried at 50^0C for 1 h in a hot air oven (Tempo Instruments and equipments Pvt Ltd). The half dried mass was pressed through a sieve of aperture size 710 μm and finally dried at 50^0C for 2 h.

*Mixing of the granules to form the multi-unit dosage form***:** The conventional (A) and the matrix granules (B) were mixed together in the ratio 1:1 (A: B). In the mixture, aliquots of the granules were selected such that the total drug content in a tablet was 300 mg; representing the contribution from A and B granules.

Tablet formulation: Different tablets were prepared using matrix granules alone and admixture of conventional and matrix granules mixed in ratio 1:1. Compression was done using a rotary compression machine (Model Riddhi, Ahmedabad) to form flat faced tablets with a diameter of 12.5mm. The weights of the tablets varied depending on the formulation. The drug contents for the sustained release and MU formulations were 400mg and 300 mg respectively. In the case of the MU formulation, magnesium stearate (0.5% w/w) and dried maize starch powder (5% w/w) were added to the granules prior to compression. The tablets were allowed to equilibrate in a dessicator 24 h before their evaluation.

Determination of tablet tensile strength (T): This is

the stress needed to fracture a tablet by diametral compression. It is given by Fell and Newton (Fell and Newton, 1977) as:

$$T = 2P/\pi Dt \quad (1)$$

where P is the fracture load that causes tensile failure of a tablet of diameter, D and thickness, t. The fracture loads (Kg) of ten tablets were determined individually with the Monsanto hardness tester, following Brook and Marshal (1968). The mean values of the fracture loads were used to calculate the T values for the various tablets.

Friability test: The friability test is to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. Five tablets were placed in the drum of a Erweka friabulator (Heusenstamm, Germany) rotating at 20 rev per min for 10 min. The percentage dust formed due to the impact was determined and taken as index of friability. The test was carried in triplicate.

In vitro dissolution test: Two tablets of the MU were placed in a cylindrical basket (aperture size 425µm: diameter 20mm; height 25mm), and immersed in 900ml of leaching fluid (0.1N hydrochloric acid maintained at 37 ±2^{o}C). The fluid was stirred at 100rpm (Model Disso 2000, Lab India). Samples of the dissolution fluid (5ml) were withdrawn at selected time intervals with a syringe fitted with a cotton wool plug and replaced with an equal volume of drug-free dissolution fluid. The samples were suitably diluted with blank dissolution fluid and were analysed for content of theophylline spectrophotometrically at λ_{max}, 272nm by using an Elico SL 210 UV-Visible double beam spectrophotometer (Elico, India). However, for the sustained as well as the market formulations only one tablet was used for the determination. The amounts released were expressed as a percentage of the drug content in the dissolution medium. The dissolution test was carried out in quadruplicate and the mean results reported.

Determination of rate order kinetics: The dissolution data were analyzed on the basis of zero order, (cumulative amount of drug released vs. time), first order rate (log cumulative amount of drug remaining vs. time) and Higuchi model (cumulative amount of drug released vs. square root of time). These are the most frequently reported kinetics of drug release from drug particles and their solid dosage forms (Higuchi , 1963; Okor, *et al.,* 1991).

The test rate order equations are:

Zero order: $m = k_0 t$ (2)

First order: $\log m_1 = \log m_0 - 0.43\, k_1 t$ (3)

Higuchi: $m = k_H t^{1/2}$ (4)

where m is the percentage (%) amount of drug released in time t; m_1 is the residual amount (%) of drug in time t; m_0 is the initial amount of drug (100%) at the beginning of the first order release; k_0, k_1 and k_H are the release rate constants for the zero, first order and the Higuchi models, respectively. The correlation coefficient (r) for each rate order was calculated. The dissolution profile was considered to follow a particular rate order if the r value was ≥ 0.95 (Uhumwangho and Okor, 2006[a]).

Differential Scanning Calorimetry (DSC): Thermograms of samples (Multiunit dose tablet, theophylline, physical mixtures of conventional formulations and sustained release formulation) were recorded on a DSC-60 (Shimadzu, Japan). Samples (3-5mg accurately weighed to 0.005mg) were placed in aluminium pans and the lids were crimped using a Shimadzu crimper. Thermal behaviour of the samples was investigated at a scanning rate of 10^0C min^{-1}, covering a temperature range of 25-300^{0}C. The instrument was calibrated with an indium standard. Inert atmosphere was maintained by purging nitrogen gas at the flow rate of 50 ml/min.

Fourier Transform Infra Red (FTIR): The FTIR spectrum of the different samples were recorded in an Infra Red spectrometer (Nicolet Magna 4R 560, MN, USA) using potassium bromide discs prepared from powdered samples.

Statistical Analysis: All data obtained were subjected to student t- test ($p < 0.05$) to test for significance of difference.

RESULTS AND DISCUSSION:

Physical parameters of the tablets: The physical parameters of the different tablet formulations are presented in Table 1. All the formulated tablets as well as the market formulations had hardness values between 1.75 -1.81MNm^{-2}. The friability percentage of both the formulated tablets as well as the market formulations were <0.3%. The high tensile strengths with low friability values indicated that the matrix former in all the formulations promoted particle deformation and bonding during tableting (Esezobo and Pipel, 1986). However, there was no statistical significant difference in the tensile strength and friability values for all the formulations ($p>0.05$).

Table 1: Physical parameters of the different tablet formulations

Different	Tensile strength	Friability

dosage forms	(MN/m^2)	(%)
MU	1.78±0.02	0.21±0.03
SR	1.81±0.04	0.18±0.02
F1	1.75±0.02	0.29±0.05
F2	1.77±0.03	0.27±0.03

Table 2: A comparison of the empirical release data m_∞, m_p, t_∞ and k_1 values for MU, formulated sustained release, two brands of market formulations (F1 and F2).

Parameters evaluated	Model	Optimized MU tablet	Formulated sustained release	Formulation F1	Formulation F2
m_∞ (%)	97*	91*	68	80	70
m_p (%)	33*	24*	6	9	7
t_∞ (h)	12*	12*	12	12	12
k_1 (h^{-1})	0.24*	0.20*	0.25	0.25	0.20

*Value of parameters that are consistent with the model.

Drug release profile of optimized Multiunit (MU), sustained release tablet (SRT) and market brands of theophylline tablets: The release profiles of the designed model, optimized MU, sustained release tablets (SRT) and the two different market brands of theophylline (F1 and F2) are presented in Fig 1. The release parameters obtained from these curves are presented in Table 2. It can be observed that the MU tablets of composition 1:1 (A: B) gave a comparable release profile with that of the MU designed model (Fig 1). The values of the release parameters for the MU tablets of composition 1:1 (A: B) being, m_p (24%), t_∞ (11 h) and k_1 ($0.20h^{-1}$) against the corresponding values for the model m_p (33%), t_∞ (12h) and k_1 ($0.24h^{-1}$) (Uhumwangho and Okor, 2007). On the other hand, the other formulations that is, the formulated SRT with carnauba wax alone and the two brands of market products (F1 and F2) gave m_p and m_∞ that were low when compared with the model (See Table 2).

For instance, the maximum release (m_∞) was observed to be 91%, 68%, 80% and 70% for MU, SRT and market formulations F1 and F2 respectively as against the set target of 97% of the model. Based on the conventional adult dose of 200 mg 4 hourly to maximum dose of 600 mg per day, the controlled release system should provide a prompt release dose of 33% in the first 1h, while the remaining 67% is released over the next 11h at an average rate of about 6.1% h^{-1} with a maximum release of 97%. It is well known that the tensile strength of a tablet can markedly affect the release rate of a drug (Capan, 1965). Usually, an increase in tensile strength of a tablet is accompanied by a decrease in release rate, due to a decrease in tablet porosity (Katikaneni, *et al.,* 1995). Since there was no significant change in the tensile strength of all the formulations studied, hence the differences in release parameters was not influenced by tablet tensile strength. However, the release patterns of all the formulations are almost similar. Correlation coefficients (r values) are presented in Table 3 which showed that the drug release was most consistent with the Higuchi diffusion mechanism ($r \geq 0.95$), indicating that drug release was essentially by a diffusion controlled mechanism (Okor, *et al.,* 1991).

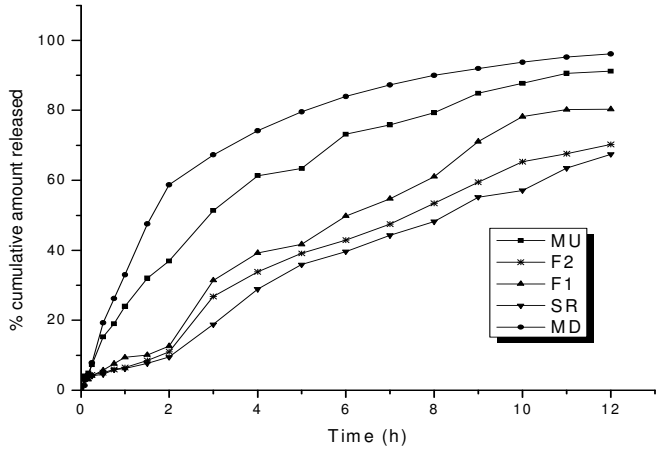

Fig 1: Cumulative percentage of theophylline released from different tablets formulations.

Note: MU = Optimised MU, MD = Designed model.

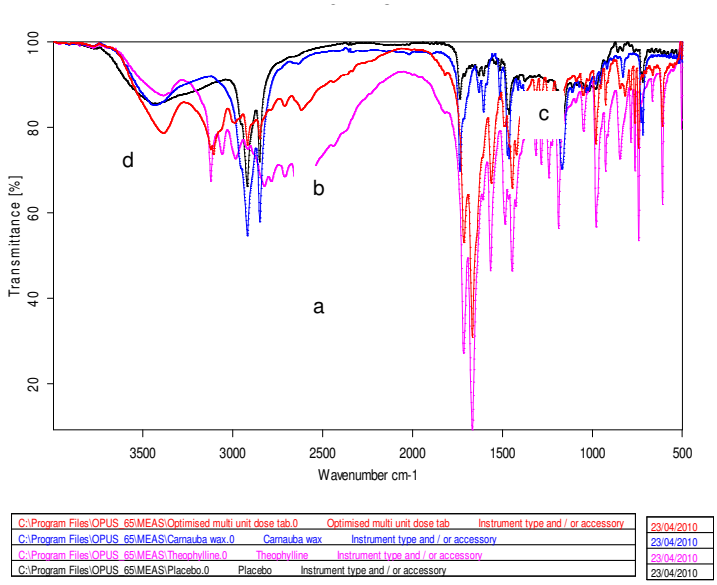

Fig 2: FTIR of (a) theophylline, (b) optimized multiunit dose, (c) placebo, (d) carnaba wax.

FTIR **:** In order to investigate if there is any interaction between added excipients and theophylline in the formulated MU tablet after compression, the FTIR of the theophylline, the MU tablet, the placebo and carnuba wax were recorded (See Fig 2a,b,c and d respectively). The IR spectrum of theophylline showed characteristic peaks at 1667.64 cm^{-1} (C=O stretch), 1556.89 cm^{-1} (C=N stretch) and (-NH stretch). However, for the placebo (carnauba wax alone with other excipients without drug), IR spectrum showed signals at 2849.30 to 2918.46 cm^{-1} (C-H stretch), 1236.63 cm^{-1} (C=O stretch). These spectra were compared with the IR spectrum of the optimized MU dosage form (that is theophylline and the carnauba wax) and represents the presence of aliphatic groups in the carnuaba wax. Moreso, at a wavelength of 1736.63 cm^{-1} it showed C=O stretch which is due to the presence of esters in the carnauba wax. All the characteristic peaks observed for both drug and excipient remained unchanged and the spectra data was superimposed (See Fig 2). This observation ruled out the possibility of chemical interaction and complex formation between the theophylline and added excipient (such as carnuba wax) during melt granulation technique to form the granules used for formation of the MU dosage tablet.

Table 3: Values of correlation coefficient (r) and release rate constants when the data were analysed according to the zero order, first order and Higuchi models.

Release kinetics	MU		SR		F1		F2	
	r	k	r	k	r	k	r	k
Zero order	0.9909	7.7	0.9945	5.7	0.9913	7.2	0.9908	6.2
First order	0.5828	0.2	0.581	0.25	0.5564	0.2	0.6572	0.2
Higuchi	0.9950	29.3	0.9753	20.5	0.9793	25.9	0.9794	22.12

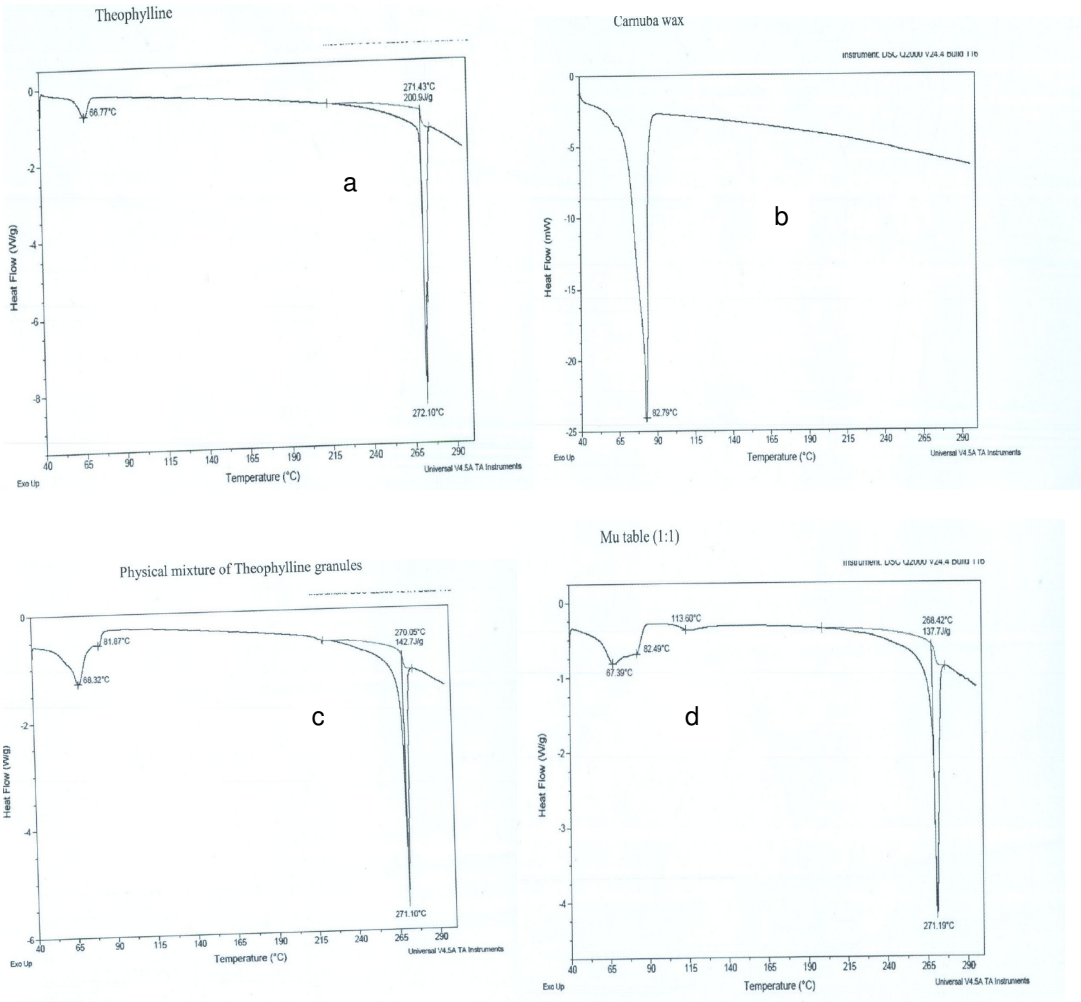

Fig 3: DSC studies of theophylline (a), carnuaba wax (b), physical mixture of theophylline and other excipients (c) and optimized multiunit dosage form (d).

*DSC***:** The DSC thermograms of the theophylline drug (a), carnuba wax (b), physical mixtures of the granules (c) and the optimized MU dosage forms (d) are presented in Fig 3. The thermogram of theophylline (Fig 3a) showed a sharp endothermic peak at 272.10^0C while that of carnauba wax showed a sharp endothermic peak at 82.79^0C (Fig 3b). The thermograms of the physical mixture of the granules and the formulated MU dosage form when compared (See Figs 3b and 3d) showed that there is no appreciable change in the thermal properties of the drug (theophylline) and the carnauba wax in the MU formulation prepared. Hence, this indicated the absence of interaction or complexation throughout the process of melt granulation and compression of the MU dosage form.

Conclusion: The study has shown that the release profile of the MU dose formulation was comparable with that of the designed model. The indication also is that the prompt release dose was determined not only by the amount of the rapid release components in the MU dose formulation but also by the amount of sustained release components, attributable to the deformation of granules of rapid into that of slow release component during tablet formulation

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REFERENCES

Peppas NA, Bures P, Leobandung W and Ichikawa H (2000). Hydrogels in pharmaceutical formulations. Eur. J. Pharm. Biopharm. 50: 27–46.

Peppas NA (2004). Intelligent therapeutics: biomimetic systems and nanotechnology in drug delivery. Adv. Drug Deliv. Rev. 56: 1529–1531.

Khan AI, Lei L, Norquist AJ and O'Hare D (2001). Intercalation and controlled release of pharmaceutically active compounds from a layered double hydroxide. Chem Commun. 22: 2342–2343.

Folloniner N and Doelker E. Biopharmaceutical comparison of oral multiple-unit and single unit sustained–release dosage forms .STP Pharma Sciences. 1992; 2: 141-155.

Vial–Bernasconi AC, Doelker E and Buri P (1988). Prolonged release Capsules; divided and monolithic forms. STP Pharma Sciences. 4: 397-409.

Ukena D, Harnest U, Sakalauskas R, Magyar P, Vetter N, Steffen H, Leichtl S, Rathgeb F, Keller A and Steinijans VW (1997). Comparison of addition of theophylline to inhaled steroid with doubling of the dose of inhaled steroid in asthma. Eur. Respir. J. 10: 2754-2760.

Hendeles L, Weinberger M and Bighlev L (1977). Absolute bioavailability of oral theophylline. Am. J. Hosp. Pharm. 34: 525-527.

Uhumwangho MU and Okor, RS (2007). Modeling of drug release from multi-unit dosage tablets of theophylline Afr. J. Biotech.: 22; 2519-2525.

Hamdani J, Moes AJ and Amighi K (2006). Development and in vitro evaluation of a novel floating multiple unit dosage form obtained by melt pelletization. Int. J. Pharm. 28: 96-103.

Uhumwangho MU and Okor RS (2006[a]). Modification of drug release from acetaminophen granules by melt granulation technique - consideration of release kinetics. Pak. J. Pharm. Sci.; 19: 22-27.

Uhumwangho MU and Okor RS (2006[b]). Studies on the compressibility of wax matrix granules of acetaminophen and their admixtures with various tableting bases. Pak J Pharm Sci.; 19: 98 – 103.

Uhumwangho MU, Okor RS and Adogah JT (2009). Potential of carnuba wax in ameliorating brittle fracture during tableting. Pak. J. Pharm. Sci. 22: 58-61.

Uhumwangho MU and Okor RS (2006[c]). Effect of matrix granulation and wax coating on the dissolution rates of paracetamol granules. Afr. J. Biotech.; 5: 766-769.

Fell JT and Newton JM (1970). Determination of tablet strength by diametral test. J. Pharm. Sci. 59: 688-689.

Brook DB and Marshall K (1968). Crushing strength of compressed tablets 1: comparison of testers. J. Pharm. Sci. 57: 481- 484.

Higuchi T (1968). Mechanism of sustained action medication. Theoretical analysis of rate release of solid drugs dispersed in solid matrices. J. Pharm. Sci. 52: 1145-1149.

Okor RS, Otimenyin S and Ijeh I (1991). Coating of certain matrix cores with aqueous – based systems of acrylate methacrylate a water – soluble copolymer and drug release profiles. J. Control. Rel. 16: 344 – 354.

Esezobo S and Pipel N (1991). The effect of temperature on the plastoelasticity of some pharmaceutical powders and on the tensile strengths of their tablets. J. Pharm.Pharmacol., 38: 409-413.

Capan, Y (1965). Influence of technological factors on formulation of sustained release tablets. Drug Dev. Ind. Pharm. 15, 927-956.

Katikaneni PR, Upadrashta, SM, Neau, SH, and Mitra AK (1995). Ethylcellulose matrix controlled release tablets of a water-soluble drug. Int. J. Pharm. 123, 119-125.